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EUROPEAN PATENT APPLICATION

(21) Application number: 94309461.5

(51) Int. Cl.⁸: **A61K 31/445, A61K 31/40**

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(30) Priority: 21.12.93 US 170606

(43) Date of publication of application:
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(84) Designated Contracting States:
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PT SE

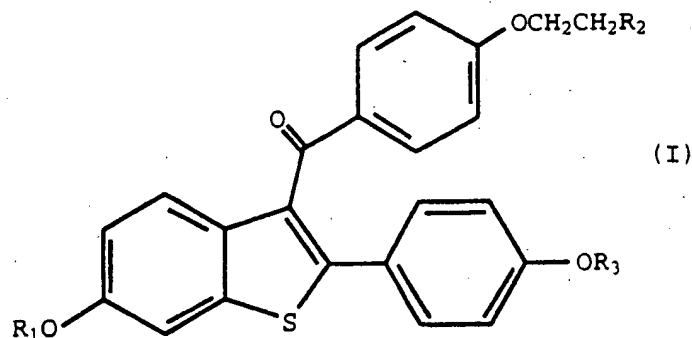
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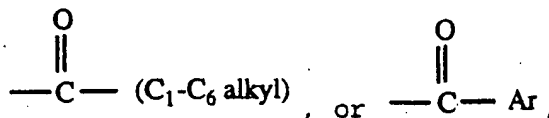
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(54) Inhibition of ldl oxidation and atherosclerosis.

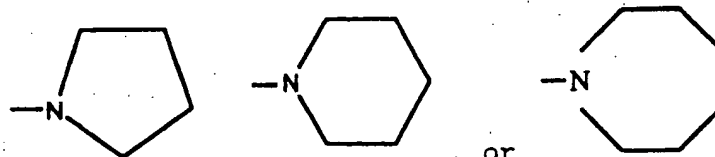
(57) Methods of inhibiting LDL oxidation, atherosclerosis, advanced glycosylation end products, and superoxide anions and other reactive oxygen intermediates, comprising administering to a human or other mammal in need of treatment an effective amount of a compound having the formula



wherein R₁ and R₃ are independently hydrogen, -CH₃,



wherein Ar is optionally substituted phenyl;
R₂ is



and

pharmaceutically acceptable salts and solvates thereof.

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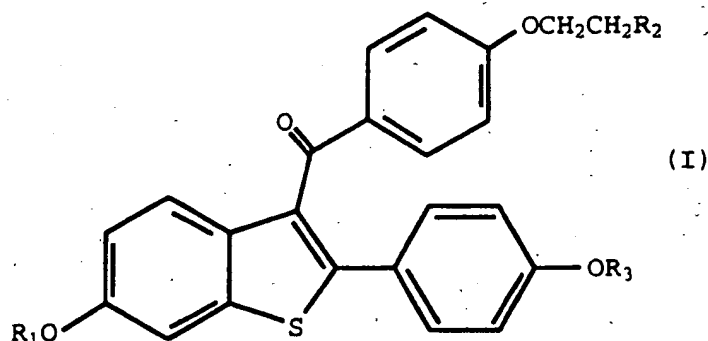
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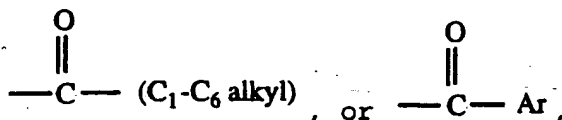
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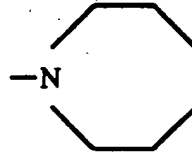
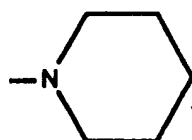
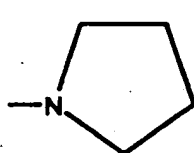
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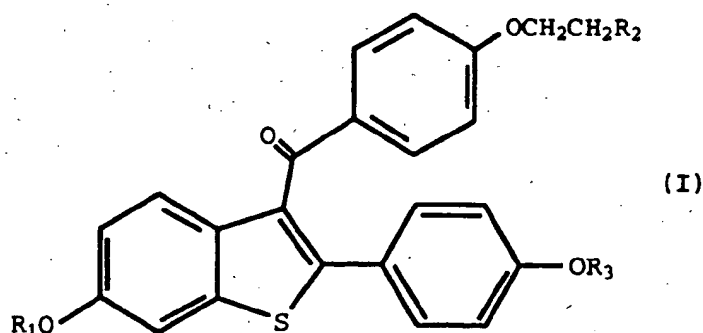
Atherosclerosis as manifested in its major clinical complication, ischaemic heart disease, continues to be a major cause of death in industrialized countries. It is now well accepted that atherosclerosis can begin with local injury to the arterial endothelium followed by proliferation of arterial smooth muscle cells from the medial layer to the intimal layer along with deposition of lipid and accumulation of macrophage derived foam cells in the lesion. As the atherosclerotic plaque develops it progressively includes more and more of the affected blood vessel and can eventually lead to ischaemia or infarction. Therefore, it is desirable to provide methods of inhibiting the progression of atherosclerosis in patients in need thereof.

There is evidence based on animal and laboratory findings that peroxidation of LDL lipid, such as the unsaturated fatty acid portions of LDL cholesteryl esters and phospholipids, facilitates the accumulation of cholesterol in monocyte/macrophages which eventually are transformed into foam cells and become deposited in the sub-endothelial space of the vessel wall. The accumulation of foam cells in the vessel wall is recognized as an early event in the formation of an atherosclerotic plaque. Thus, it is believed that peroxidation of LDL lipid is an important prerequisite to the facilitated accumulation of cholesterol in the vessel wall and the subsequent formation of an atherosclerotic plaque. For example, it has been shown that monocyte/macrophages take up and degrade native LDL at relatively low rates and without marked accumulation of cholesterol. In contrast, oxidized LDL is taken up by these monocyte/macrophages at much higher rates and with marked accumulation of cholesterol (Parthasarathy *et al.*, *J. Clin. Invest.* 77, 641 (1986)). It is therefore desirable to provide methods of inhibiting LDL lipid peroxidation in a patient in need thereof.

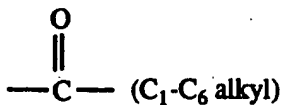
It has been shown that 2,2'-bis(3,5-di-tertiary-butyl-4-hydroxyphenylthio)propane (also known as probucol), which is a known antioxidant, may prevent the progression of atherosclerosis in a manner which is independent of its effect on lowering plasma cholesterol levels [See Kita *et al.* *Proc. Natl. Acad. Sci. USA* 84, 5928 (1987); Carew *et al.*, *Proc. Natl. Acad. Sci. USA* 84, 7725, (1987)]. It is believed that antioxidants, such as probucol, may prevent or inhibit the development of atherosclerosis by inhibiting the peroxidation of LDL and thus preventing the facilitated accumulation of cholesterol in monocyte/macrophages which eventually are transformed into foam cells and become deposited in the sub-endothelial space of the vessel wall [See Parthasarathy *et al.* *J. Clin. Invest.* 77, 641 (1986)]. Accordingly, it is desirable to provide a method of inhibiting the peroxidation of LDL.

The present invention relates to certain compounds which are useful as inhibitors of LDL lipid oxidation, atherosclerosis, advanced glycosylation end products (AGE) or glycation of AGE proteins, and superoxide anions and other reactive oxygen intermediates.

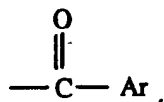
The invention provides a method of inhibiting LDL oxidation, atherosclerosis, AGE, and superoxide anions and other reactive oxygen intermediates in a human or other mammal subject comprising administering to said subject a pharmaceutically effective dose of a compound of the formula



wherein R_1 and R_3 are independently hydrogen, $-CH_3$,

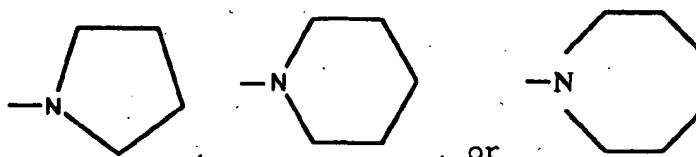


or



wherein Ar is optionally substituted phenyl;

R₂ is



or

and

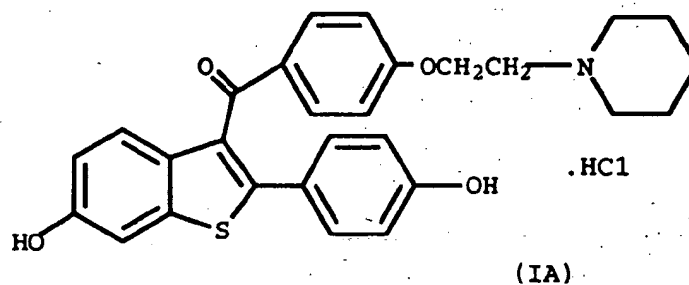
pharmaceutically acceptable salts and solvates thereof.

The current invention concerns the discovery that a select group of compounds, those of formula I, are useful for inhibiting LDL oxidation, atherosclerosis, AGE, and superoxide anions and other reactive oxygen intermediates. The methods of treatment provided by this invention are practiced by administering to a human or other mammal in need a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit the above. The term inhibit is defined to include its generally accepted meaning which includes prophylactically treating a human subject to incurring one of the above and holding in check and/or treating an existing problem listed above. As such, the present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated as sustained release dosage forms and the like.

The compounds of formula I used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The starting compound is protected, acylated, and deprotected to form the formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above. Optionally substituted phenyl includes phenyl and phenyl substituted once or twice with C₁-C₆ alkyl, C₁-C₄ alkoxy, hydroxy, nitro, chloro, fluoro, or tr(chloro or fluoro)methyl.

Included in the invention is the use of the following compound, known as raloxifene:



The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanolic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hy-

droxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β -hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methane-sulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferable salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates and bicarbonates, as well as aliphatic and aromatic amines, aliphatic diamines and hydroxy alkylamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylene diamine, cyclohexylamine and ethanolamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as agaragar, calcium carbonate, and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

Atherosclerosis is a disease state characterized by the development and growth of atherosclerotic lesions or plaque. The identification of those patients who are in need of treatment for atherosclerosis is well within the ability and knowledge of one skilled in the art. For example, individuals who are either suffering from clinically significant atherosclerosis or who are at risk of developing clinically significant atherosclerosis are patients in need of treatment for atherosclerosis. A clinician skilled in the art can readily determine, by the use of clinical tests, physical examination and medical/family history, if an individual is a patient in need of treatment for atherosclerosis.

An effective antiatherosclerotic amount of a compound of formula (1) is an amount which is effective in inhibiting development or growth of atherosclerosis in a patient in need thereof. As such, successful treatment of a patient for atherosclerosis is understood to include effectively slowing, interrupting, arresting, or stopping atherosclerotic lesion or plaque development or growth and does not necessarily indicate a total elimination of the atherosclerosis. It is further understood and appreciated by those skilled in the art that successful treatment for atherosclerosis can include prophylaxis in preventing atherosclerotic lesion or plaque formation.

As the compounds described inhibit the oxidation of LDL induced by copper or by macrophage based oxidation, the use of the invention encompasses the inhibition or the formation of advanced glycosylation end products (AGE) including the glycation of proteins such as AGE-albumin, AGE-collagen, and AGE-LDL. For example, cardiovascular complications observed in diabetics is believed to be due, at least in part, to increased amounts of AGE-modified proteins. Therefore, the invention encompasses inhibiting diseases to which elevated AGE modified protein levels contribute.

The invention also encompasses the inhibition of superoxide anions, and other reactive oxygen intermediates (ROI) levels/amounts. The compounds, due to their free radical scavenging abilities, are believed to be

useful in such instances as inhibiting Acute Respiratory Distress Syndrome, the systemic inflammatory response often observed following cardiopulmonary bypass surgery, pancreatitis, and long term respiratory therapy problems associated with high oxygen levels.

5 Peroxidation of LDL lipid, such as the unsaturated fatty acid portions of LDL cholesteryl esters and phospholipids, is known to facilitate the deposition of cholesterol in macrophages which subsequently are deposited in the vessel wall and are transformed into foam cells. The identification of those patients who are in need of inhibition of peroxidation of LDL lipid is well within the ability and knowledge of one skilled in the art. For example, those individuals who are in need of treatment for atherosclerosis as defined hereinabove, are also patients who are in need of inhibition of peroxidation of LDL lipid. An effective antioxidant amount of a compound of formula (1) is an amount which is effective in inhibiting the peroxidation of LDL lipid in the patient's blood.

10 An effective dose of the compounds described for the complications listed can be determined by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to: the species of patient; its size, age and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

15 Generally accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need of treatment from once to about three times each day, or more often as needed to effectively inhibit one of the listed problems.

20 It is usually preferred to administer a compound of formula I in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group, such as the piperidino ring. It is also advantageous to administer such a compound by the oral route. For such purposes the following oral dosage forms are available.

Formulations

30 In the formulations which follow, "Active ingredient" means a compound of formula I.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

35

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
40 Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

45 The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Examples of specific capsule formulations of the compound of formula 1 wherein the compound is raloxifene, include those shown below:

50

55

Formulation 2: Raloxifene capsule

	Ingredient	Quantity (mg/capsule)
5	Raloxifene	1
	Starch, NF	112
	Starch flowable powder	225.3
10	Silicone fluid 350 centistokes	1.7

Formulation 3: Raloxifene capsule

	Ingredient	Quantity (mg/capsule)
15	Raloxifene	5
	Starch, NF	108
20	Starch flowable powder	225.3
	Silicone fluid 350 centistokes	1.7

Formulation 4: Raloxifene capsule

	Ingredient	Quantity (mg/capsule)
30	Raloxifene	10
	Starch, NF	103
	Starch flowable powder	225.3
35	Silicone fluid 350 centistokes	1.7

Formulation 5: Raloxifene capsule

	Ingredient	Quantity (mg/capsule)
40	Raloxifene	50
	Starch, NF	150
45	Starch flowable powder	397
	Silicone fluid 350 centistokes	3.0

50 The specific formulations above may be changed in compliance with the reasonable variations provided.
A tablet formulation is prepared using the ingredients below:

55

Formulation 6: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

Formulation 7: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 mL dose are made as follows:

Formulation 8: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

TEST PROCEDURES**Assay 1**

5 The thiobarbituric acid assay as described by Schuh *et al.*, (PNAS 75: 3173, 1978) and modified by Morel
et al., (Lab Invest 55: 419, 1986) was used to determine the degree of inhibition of LDL peroxidation by estradiol
 and Compound A of the invention. A 1 ml solution containing 250 micrograms (μg) of LDL with either estradiol
 or Compound A of the invention in amounts varying from 1-30 μM is incubated for 5-18 hrs at 37 degrees C
 10 in the presence of 5 μM CuSO_4 . Following incubation, 1 ml of 25% trichloroacetic acid and 1 ml of 1% thiobar-
 bituric acid is added. All samples are boiled for 45 minutes and fluorescence is measured at 515 nm excitation
 and 553 nm emission wavelengths.

(Compound A is a compound of formula 1 wherein R_1 and R_3 are hydrogen, and R_2 is 1-pyrrolidino).

TBAR UNITS				
Conditions	25 μM	5 μM	1 μM	0 μM
Compound A	78	109	142	356
Estradiol	160	153	259	356
Control (no copper)	90	90	90	90

Assay 2

25 Resident macrophages from the mouse peritoneal cavity were plated at 1×10^6 cells per well in F10 media
 without serum. LDL which had been dialyzed and filtered through a 0.2 micron filter were added to each well
 at a final concentration of 1 mg/ml (500 μg added per well) and macrophages were treated with 1- 5 μM of Com-
 30 pound A or control for 24 hrs. The wells designated media alone represents LDL incubated overnight on the
 same plate with F10 media without cells. This value was subtracted from the TBAR values obtained in the pres-
 ence of resident macrophages and reflects the extent of cellular modification of LDL.

Conditions	TBAR Units
Control	130
Compound A 5 μM	30
Compound A 2.5 μM	75
Compound A 1 μM	129
Estradiol 25 μM	30

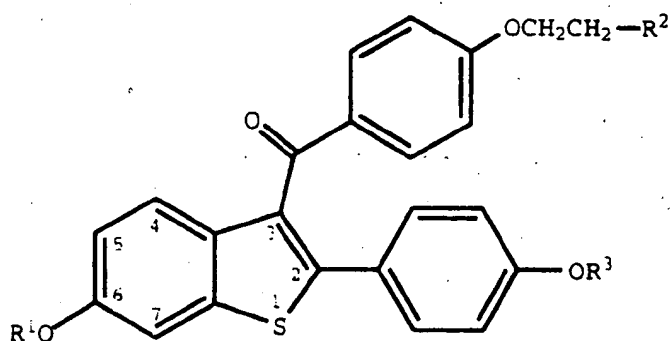
Claims

1. The use of a compound having the formula

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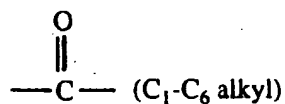
15



(I)

wherein R¹ and R³ are independently hydrogen, -CH₃,

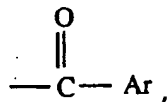
20



25

or

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wherein Ar is optionally substituted phenyl;

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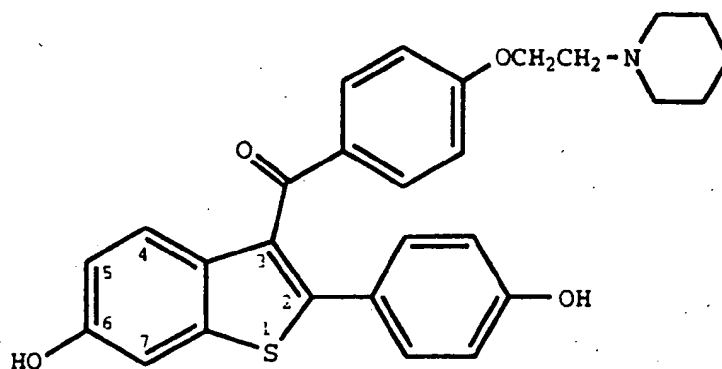
R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting LDL oxidation.

2. The use of Claim 1 wherein said compound is

40

45

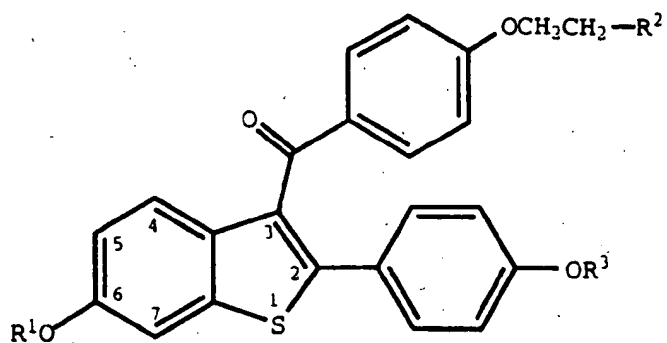
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or its hydrochloride salt.

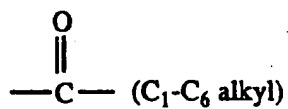
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3. The use of a compound having the formula

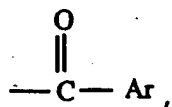


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wherein R¹ and R³ are independently hydrogen, -CH₃,



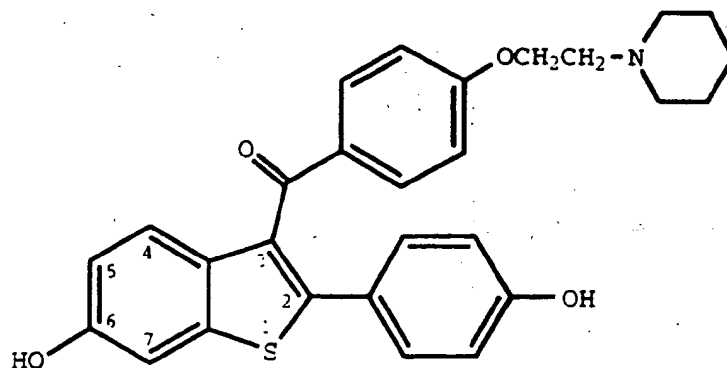
or



wherein Ar is optionally substituted phenyl;

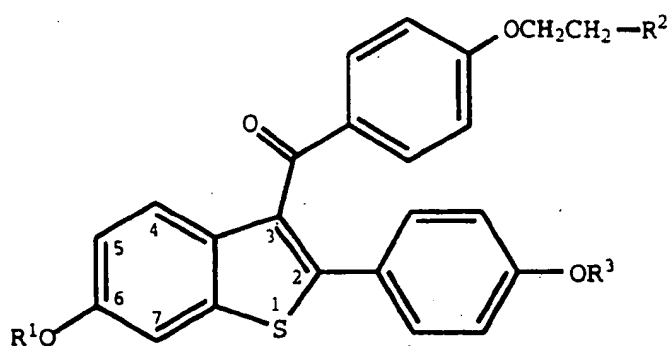
R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting atherosclerosis.

4. The use of Claim 3 wherein said compound is



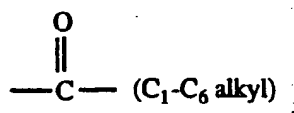
or its hydrochloride salt.

5. The use of a compound having the formula

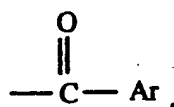


(I)

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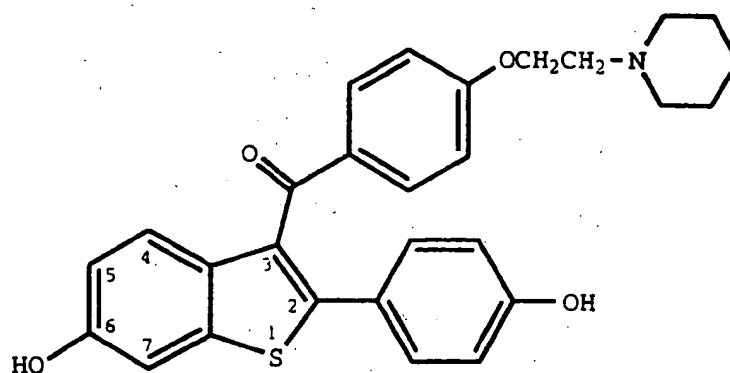
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wherein Ar is optionally substituted phenyl;

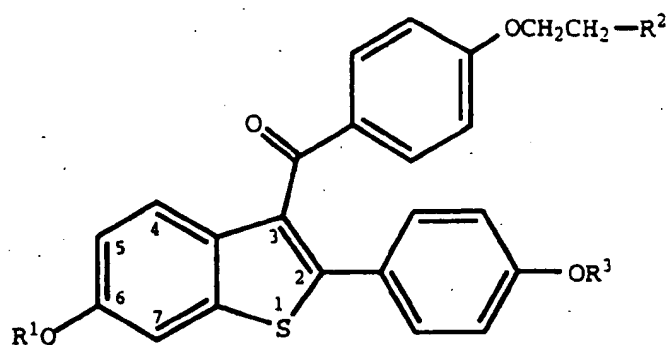
R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting ischaemic heart disease.

6. The use of Claim 5 wherein said compound is



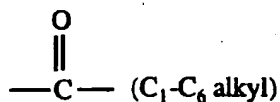
or its hydrochloride salt.

7. The use of a compound having the formula

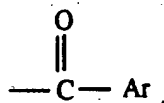


(I)

wherein R¹ and R³ are independently hydrogen, -CH₃,



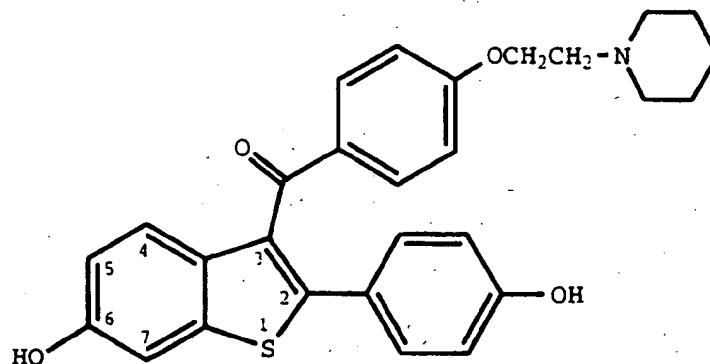
or



wherein Ar is optionally substituted phenyl;

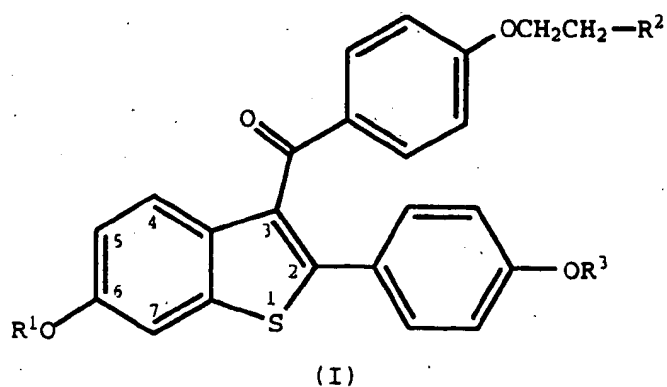
R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting superoxide anions and other reactive oxygen intermediates.

8. The use of Claim 7 wherein said compound is

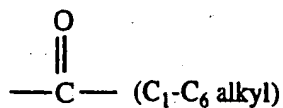


or its hydrochloride salt.

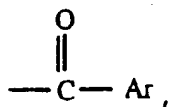
9. The use of a compound having the formula



wherein R¹ and R³ are independently hydrogen, -CH₃,



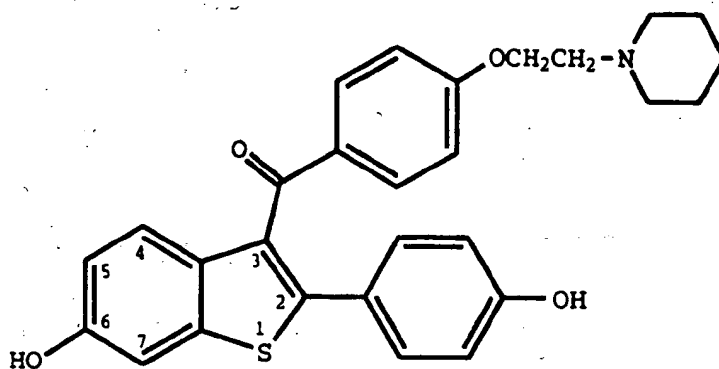
25 or



wherein Ar is optionally substituted phenyl;

R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting advanced glycosylation end products.

10. The use of Claim 9 wherein said compound is



or its hydrochloride salt.



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 94 30 9461

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
P,X	DATABASE DIALOG FILE 129: PHIND Knight-Ridder Information Accession No. 00405104, *on-line abstract* & SCRIP, vol. 1932, 17 June 1994 page 29 'Lilly's Gemzar - US new drug application in 1994?'	1-4	A61K31/445 A61K31/40
P,Y	EP-A-0 605 193 (ELI LILLY CO.) 6 July 1994 * page 2, line 7 - line 9; claims 1-3 *	1-4	
Y	ENDOCRINOLOGY, vol. 111, no.6, 1982 pages 2046-2054, H.S. KEEPING ET AL. 'Modulation of rat uterine progesterone receptor levels and peroxidase activity by tamoxifen citrate, LY117018, and estradiol' * abstract *	1-10	
Y	DATABASE DIALOG FILE 445:R&D FOCUS IMSworld Publications Ltd. Dialog Accession no. 00004016, * abstract * & R&D FOCUS DRUG NEWS, 6 September 1993 'Products nearing market with Lilly'	5-10	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
A	US-A-3 983 245 (LADD) * abstract *	5	
-/-			
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 4 April 1995	Examiner Foerster, W
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			

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EUROPEAN SEARCH REPORT

Application Number
EP 94 30 9461

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	<p>DATABASE FILE 187, FDC REPORTS Dialog Information Services 1987-1993, Accession No. 00089403, *on-line abstract* & THE PINK SHEET, vol. 55, no.16, 19 April 1993 'Lilly's raloxifene entering phase III for osteoporosis'</p> <p>-----</p>	1,2	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 4 April 1995	Examiner Foerster, W
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>			

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